REMARKS

Subsequent to the filing of an Appeal Brief by Applicants herein on March 25, 2005, the finality of the previous Office Action was withdrawn and the new current non-final Office Action issued. Claims 1-5 remain pending for prosecution in this application.

The Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1-5 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse the rejection.

In support of the outstanding rejection, the Examiner makes reference to the teachings in the present specification showing that mRNA encoding the protein shown as SEQ ID NO:60 (referred to in the present specification as "PRO1291") is significantly upregulated in certain types of human cancer tissue as compared to the respective normal, non-cancerous human tissue (see the present Office Action at page 3, first paragraph). Notwithstanding these data evidencing significant and detectable mRNA upregulation, however, the Examiner asserts that "elevated protein levels cannot be accurately predicted solely on elevation of mRNA levels", and therefore, the Examiner concludes that the specification does not teach "how to use" the presently claimed anti-PRO1291 antibodies. Applicants respectfully disagree.

A. Procedural and Legal Standards For Making Rejections Under 35 U.S.C. §§ 101 and 112

Section 706 of the Manual of Patent Examining Procedure (MPEP) deals specifically with the proper procedure that is to followed by a patent examiner in setting forth a rejection of a claimed invention during *ex parte* examination. Specifically, MPEP § 706 makes clear that if a rejection of a claim is to be made, it is initially required that a patent examiner make a satisfactory *prima facie* case supporting the rejection. Once such a *prima facie* case is made, the burden then shifts to the patent applicant to rebut the *prima facie* case made by the examiner. As such, the initial step in setting forth a valid rejection of a claimed invention is that the examiner must make a valid *prima*

facie case supporting the rejection.

> What constitutes a valid *prima facie* case? Guidance is found in MPEP § 706(I) which states:

> "[t]he standards of patentability applied in the examination of claims must be the same throughout the Office....The standard to be applied in all cases is the "preponderance of the ·evidence" test. In other words, <u>an examiner should reject a claim if, in view of the prior art and the evidence of record, it is more likely than not that the claim is unpatentable.</u>" (Emphasis supplied).

As such, it is clear that in order to satisfy the requirement of making a valid *prima facie* case in support of a rejection, the Examiner must show that upon consideration of the totality of data and evidence, it is <u>more likely than not</u> that the reasoning underlying the rejection is correct. Therefore, given the Examiner's rationale underlying the present rejection, in order to satisfy the requirement of making a valid *prima facie* case, the Examiner <u>must</u> show that it is more likely than not that no correlation exists between (1) the level of mRNA encoding the PRO1291 protein shown as SEQ ID NO:60 and (2) the PRO1291 protein shown as SEQ ID NO:60 itself. Applicants respectfully submit that the Examiner has failed to make such a *prima facie* case herein and, therefore, the outstanding rejection should be withdrawn.

B.   The Scientific Data At Issue

As described above, the Examiner concedes that the present specification teaches that mRNA encoding the PRO1291 protein shown as SEQ ID NO:60 is significantly upregulated in certain human lung and esophageal tumor types as compared to the respective normal human tissue (see the present Office Action at page 3, first paragraph). More specifically, the data is Example 18 of the present specification clearly demonstrate that mRNA encoding the PRO1291 protein of SEQ ID NO:60 is significantly and reproducibly upregulated in cancerous lung- and esophageal-derived tumors as compared to normal non-cancerous human lung and esophageal tissue, respectively. Based upon these data, Applicants have asserted that the observed differential expression of the mRNA encoding the PRO1291 protein of SEQ ID NO:60 and, consequently, the PRO1291 protein of SEQ ID NO:60 itself, is useful for diagnosing the presence (or absence) of certain lung- and

esophageal-derived tumors in humans.

As described above, however, the Examiner alleges that there is no generally recognized correlation between mRNA levels and the levels of protein expressed from that mRNA. For example, in the present Office Action, the Examiner states:

"it is well known that mRNA is not a reliable indicator of increased protein expression". (emphasis supplied, see Office Action at page 3, first full paragraph).

The Examiner also states:

"[s]cientific literature from several different fields has established that elevated protein levels cannot be accurately predicted solely on elevation of mRNA levels". (see Office Action at page 3, first full paragraph).

Finally, the Examiner cites to certain references which allegedly show a lack of correlation between mRNA levels and expressed protein levels and then states:

"[t]here is a very low correlation, if any at all....between mRNA and protein level in liver". (see Office Action at page 3, first full paragraph).

It appears, however, that the Examiner is employing an incorrect legal standard to support the outstanding rejection. The Examiner appears to be requiring that the Applicant demonstrate that mRNA levels always correlate with expressed protein levels. By citing to specific situations which allegedly teach a specific lack of correlation between mRNA levels and levels of protein expressed from that mRNA, the Examiner concludes that the current rejection under 35 U.S.C. § 112, first paragraph, is proper. However, as described above, the proper legal standard to be applied requires the Examiner to make a valid *prima facie* case, i.e., to show that it is "more likely than not" that mRNA levels in general are not predictive of the level of protein expressed from that mRNA. More specifically, a proper *prima facie* case herein would require the Examiner to show that it is more likely than not that mRNA levels encoding the PRO1291 protein of SEQ ID NO:60 are not predictive of the level of PRO1291 protein expressed from that specific mRNA. Applicants respectfully submit that the Examiner has fallen well short of making this showing and, therefore, has failed to make a valid *prima facie* case to support the outstanding rejection.

In regard to the Examiner's support for the outstanding rejection, Applicants concede that there are certain examples of where the level of mRNA does _not_ correlate with the level of protein expressed from that mRNA in a particular cell type. Certainly, such examples are known in the art and the Examiner has cited to a few of them as described above. However, Applicants wish to point out that these are _individual, specific instances_ where such a correlation does not appear to exist. These citations do not teach anything about whether a correlation exists between mRNA levels and expressed protein levels _generally_ (i.e., for most or all of the estimated 80,000-100,000 expressed human genes in the human genome). More accurately, these specific citations do _not_ show that it is _more likely than not_ that a correlation does not exist between mRNA levels encoding SEQ ID NO:60 and the level of PRO1291 protein expressed therefrom. Thus, the Examiner has failed to make the requisite _prima facie_ case to support the outstanding rejection.

Contrary to the Examiner's assertion, Applicants respectfully submit that it is widely known and well accepted in the scientific research community that there is a strong, general correlation between the amount of mRNA in a particular cell type and the amount of protein expressed from that mRNA for any particular gene of interest (with certain specific exceptions as alluded to above). In this regard, Applicants first note that the sale of gene expression microchips is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars in sales of their GeneChip arrays in 2004. As is well known in the industry, the primary use for these gene expression chips is to quantitatively measure the amount of gene expression in a sample _at the mRNA level_. Applicants wonder why the use of such gene expression chips would be so prevalent in the biotechnology research industry if mRNA levels measured using these chips were not generally predictive of the level of the protein expressed from that mRNA. Certainly, the research community believes that the information obtained from these chips is useful (_i.e., that it is more likely than not informative of the expressed protein level_) because if is were not, why would the sales of such allegedly "non-informative" research tools be so successful? Therefore, the Examiner's statement in the present Office Action that "it is well known that mRNA is not a reliable indicator of increased protein expression" is certainly untrue.

Additionally, enclosed is a Declaration by Dr. Paul Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the tumor antigen project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the tumor antigen project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceeds this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Finally, Applicants would like to direct the Examiner's attention to the enclosed Lockhart and Winzeler article entitled "Genomics, Gene Expression and DNA Arrays", published in the esteemed scientific journal Nature. Unlike the articles cited by the Examiner in support of the outstanding rejection (which, as described above, relate to individual, specific genes and not to gene

expression in general), the Lockhart and Winzeler article presents a much more global, general view

on techniques for quantitatively measuring mRNA and how those measurements provide information

on the proteins encoded thereby. Most informatively, Lockhart and Winzeler state:

> "[a]mong the most powerful and versatile tools for genomics are high-density arrays of oligonucleotides or complementary DNAs....[o]ne of the most important applications for arrays so far is the monitoring of gene expression (mRNA abundance)." (see page 827, columns 1 and 2).

Applicants wonder why these high density cDNA arrays and the use thereof for quantitatively

measuring mRNA would be such a "powerful and versatile tool" if there were no generally accepted

correlation between mRNA and protein as is suggested by the Examiner herein? Applicants also

wonder why the worldwide sales of these high-density arrays for use in measuring mRNA levels

would be so successful (as described above) if there were no generally accepted correlation between

mRNA and protein as is suggested by the Examiner herein? The clear answer is that, contrary to the

Examiner's assertion, in the vast majority of cases, there is a strong, widely-understood and accepted

correlation between the levels of mRNA and the levels of protein encoded thereby.

In fact, this conclusion is explicitly stated by Lockhart and Winzeler on page 830, where the

authors state:

> "[b]ut if messenger RNA is only an intermediate on the way to production of the functional protein products, why measure mRNA at all? One reason is simply that protein-based approaches are generally more difficult, less sensitive and have a lower throughput than RNA-based ones. But more importantly, mRNA levels are <u>immensely informative</u> about cell state and the activity of genes, and for **most** genes, <u>changes in mRNA abundance are related to changes in protein abundance.</u>" (Emphasis supplied).

As such, the authors <u>explicitly</u> set forth the conclusion that <u>"more often than not" (i.e., for "most"</u>

<u>genes),</u> there is a correlation between mRNA levels and the amount of protein encoded thereby and,

therefore, quantitative measurement of mRNA is "<u>immensely informative</u>".

Taken together, the totality of the evidence presented herein suggests that although there are

some examples in the scientific art that do not fit within the central dogma of molecular biology that

there is a correlation between polypeptide and mRNA levels, <u>these instances are exceptions rather</u>

than the rule. Thus, one skilled in the art would reasonably expect in this instance, based upon (1) the data shown in the specification for the PRO1291 protein of SEQ ID NO:60 and the mRNA encoding it and (2) the above described evidence demonstrating that it is well understood and accepted in the research community that in more cases than not, there exists a quantitative correlation between levels of mRNA and levels of the protein encoded by that mRNA, that it is more likely than not that the PRO1291 protein of SEQ ID NO:60 is overexpressed, just as is the mRNA encoding the PRO1291 protein of SEQ ID NO:60. Accordingly, Applicants submit that the currently claimed anti-PRO1291 antibodies are useful in the diagnosis of certain types if human lung and esophageal cancer and based on such utility, one of skill in the art would know exactly how to use such antibodies for diagnosis of such cancers.
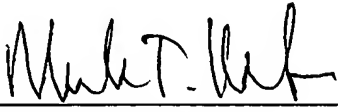
In summary, the present specification provides actual scientific data demonstrating that mRNA encoding the PRO1291 protein of SEQ ID NO:60 is differentially expressed in certain types of human cancer tissue as compared to the respective normal human tissue. The legal and scientific analysis provided above (in association with the enclosed declaration and scientific review article) clearly demonstrate that it is more likely then not that the observed differential expression pattern observed for PRO1291 mRNA would also apply to PRO1291 protein encoded by that mRNA. As such, Applicants respectfully submit that the outstanding rejections are improper and should be withdrawn.

In light of the above amendments and remarks, Applicants believe that this application is now in condition for immediate allowance and respectfully request that the outstanding rejections be withdrawn and this case passed to issue.

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The Examiner is invited to contact the undersigned at (650) 225-4461 if any issues may be resolved in that manner.

Respectfully submitted,

GENENTECH, INC.

By: _____
Mark T. Kresnak, Ph.D.
Reg. No. 42,767
Phone: (650) 225-4461
Fax: (650) 952-9881